Immune reconstitution in human immunodeficiency virus-positive patients on highly active antiretroviral therapy at an urban public sector district hospital

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Immune reconstitution is measured by circulating CD4 T cells that follows a biphasic pattern. Not everyone who is on highly active antiretroviral therapy (HAART) will attain immune reconstitution at the same rate, or to the same extent. This study aimed to describe the patterns of immune reconstitution in an urban public district hospital. A retrospective review of clinical files was performed on 354 patients who maintained virological suppression to < 50 copies/ml over three years, following the initiation of HAART. Changes in CD4 T-cell count were described using descriptive statistics. Non-parametric analysis was conducted. Ninety-four per cent (n = 334) of patients had a baseline CD4 count ≤ 200 cells/ul, while only 0.3% (n = 1) had a baseline > 350 cells/ul. The CD4 count increased from a median baseline of 92 cells/ul to 429 cells/ul over the three-year period. The CD4 count increased by 184 cells/ul, 72 cells/ul and 62 cells/ul in the first, second and third years, respectively. At the last determination, 37.3% (132) had a CD4 count ≥ 500 cells/ul and 6.8% (24) had a CD4 count < 200 cells/ul. Females had a statistically significant (p-value < 0.001) overall increase of 349 cells/ul, compared to the 273 cells/ul seen in males. Only 27.6% (53) of patients with a baseline CD4 cell count < 100 cells/ul were able to attain levels ≥ 500 cells/ul. Despite the good response to HAART, patients with a baseline CD4 cell count < 100 cells/ul were less likely to attain a normal CD4 count after three years of virological suppression on HAART than those with a higher baseline.

Introduction

The prognosis and life expectancy of persons infected with the human immunodeficiency virus (HIV) has been significantly improved with the advent of highly active antiretroviral therapy (HAART).[1] The life expectancy of people living with HIV has increased by as much as 25 years, compared to 5-10 years from the time of infection prior to the availability of HAART, if they are treated appropriately.[2]

If left untreated, the progressive reduction of CD4 T lymphocytes is the major distinctive attribute of an HIV-1 infection. This happens as a result of viral replication and the resulting cytolysis and programmed cell death.[3,4] HAART reduces morbidity and mortality in HIV-positive individuals by causing virological suppression, an increase in the CD4 T-cell count and partial reversal of HIV-1-associated immunological disorders.[5-7]

Immune reconstitution is characteristically measured by circulating CD4 T-cell count, which follows a biphasic pattern, with an initial rapid rise in the CD4 T-cell count during the first few months of HAART, followed by a slower rise.[8] In the majority of studies, patients who are virologically suppressed on HAART will experience a fast rise in CD4 T cells in the first three months, followed by a more gradual rise in CD4 T cells over the next 2-3 years, after which changes to the CD4 T-cell count are less predictable.[6] Some researchers have reported a sustained increase in CD4 T cells for up to four years, while others have reported little or no change beyond 3-4 years of HAART.[1,5,8-10] By extrapolation, measuring CD4 to quantify immune reconstitution allows the success of the treatment to be assessed.

Not every individual who is on HAART will attain immune reconstitution at the same rate, or to the same extent.[11] Several factors influence immune reconstitution, including a lower baseline CD4 T-cell count prior to the initiation of HAART, being older, a degree of immune activation, altered T-cell homeostasis and HIV co-receptor usage, all of which are predictors of poor immune reconstitution.[2] Gender and the degree of immunosupression prior to commencing HAART have also been known to modify immune reconstitution.[10]

Numerous studies on factors that modify immune reconstitution have demonstrated that CD4 nadir is the most consistent predictor of immune reconstitution, which is why absolute CD4 T-cell count has been chosen as the main determinant of HAART initiation.[2,5] World Health Organization (WHO) guidelines suggest treatment should be commenced before a CD4 T-cell count of less than or equal to 500 cells/ul, which is in keeping with the recommendation of the European AIDS Clinical Society guideline.[4,12] The 2010 South African National Department of Health guidelines recommended the treatment of pregnant women and patients with tuberculosis co-infection when their CD4 T-cell count was less than or equal to 350 cells/ul, irrespective of their WHO clinical stage. An amendment to this in the 2013 guideline now recommends treatment of all patient with a CD4 T-cell count of 350 cells/ul and

below.[13,14] CD4 T cells plateau within the normal range in the majority of patients who are virologically suppressed while on HAART, but in a few patients, CD4 T cells plateau below 500 cells/ul, which is the lower limit of normal.[1,7,15] HIV-positive patients are more likely to develop acquired immune deficiency syndrome (AIDS)-defining illnesses and non-AIDS defining illness at a CD4 T-cell count of less than 500 cells/ul, despite the attainment of complete virological suppression.[15-17]

Immune reconstitution in HIV-positive patients on HAART in KwaZulu-Natal has not been studied. Given the clinical importance of achieving a normal CD4 T-cell count, this study aimed to describe the pattern of immune reconstitution in HIV-positive patients initiated on HAART at an urban public sector district hospital antiretroviral (ARV) clinic in KwaZulu-Natal.

Method

This was a retrospective observational analytical study that reviewed the clinical notes of patients who had been initiated on HAART between 1 January 2007 and 31 December 2010.

The study population consisted of HIV-positive patients who were commenced on HAART at this ARV clinic, which is managed by the doctors of a non-governmental organisation in collaboration with the doctors at this hospital. The clinic is located in the Ethekwini Municipality of KwaZulu-Natal. During this period, 2 217 ARV-naive patients were initiated. HAART was defined as a protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI) combined with two nucleoside reverse transcriptase inhibitors. For the purposes of this study, non-responders were defined as those with a CD4 T-cell count < 200 cells/ul, despite virological suppression on HAART.

Patients were included if they were aged 18 years and older, ARV drug-naive prior to the initiation of HAART, and had had their CD4 T-cell count documented in the first six months after initiating HAART, and then at least annually for three years. These patients also needed to have had an HIV RNA viral load of less than 50 copies/ml within six months of commencing HAART, and to have maintained this viral suppression for the duration of the treatment. Viral load was measured at the sixth month, first year, second year and third year following commencement of HAART. Patients who met the inclusion criteria were censored at their three-year anniversary of commencing HAART.

Patients who were excluded were those who did not sustain viral suppression, had interrupted treatment during therapy, and who had failed to achieve virological suppression from the first regimen so that they were initiated on a second-line regimen. Patients who had transient elevations of an HIV RNA viral load greater than 50 copies/ml, and whose results were missing from their records, were also excluded.

Data were obtained over a two-month period (March and April 2013) using a 14-item data tool developed using input from previous similar studies.[1,3,5-7,10] Information collected included demographic (age and gender), clinical (AIDS-defining illness at the time of HAART initiation) and laboratory data (CD4 T-cell count at baseline, the sixth month, first year, second year and third year).

Quantitative variables were described using median and percentiles (25-75%), and categorical variables using frequencies and percentages. The increase in the CD4 T-cell count in the first six months, then annually until the third year (the last determination) on HAART was determined collectively, as well as for four groups, according to the baseline CD4 T-cell count (CD4 ≤ 50, 51-100,101-200 and > 200 cells/ul).

The percentage of patients with CD4 T-cell count < 200 cells/ul and ≥ 500 cells/ul at the last determination was determined for the whole group, as well as for the baseline CD4 cell strata.

The overall increase in CD4 T-cell count for the three-year duration on HAART was determined for the whole group, as well as for the baseline CD4 strata. Additional stratification variables for the overall increase in CD4 T-cell count included gender (male versus female), age (< 50 years versus > 50 years),[18] an AIDS-defining illness, pulmonary tuberculosis and the presence of hepatitis B co-infection on commencement of HAART. Since an increase in the CD4 T-cell count was used as a measure of immune recovery following HAART[4] to determine factors that had a positive impact on immune reconstitution, the overall increase in the CD4 T-cell count was analysed for each stratification variable using the Mann-Whitney U test for categorical variables with two levels, and the Kruskal-Wallis test for variables with more than two levels. A p-value of ≤ 0.05 was considered to be statistically significant. The baseline HAART regimen was not analysed as all of the patients were commenced on an NNRTI-based regimen. Statistical analysis was performed using SPSS® version 21.

This research was approved by the Biomedical Research Ethics Committee and the Post Graduate Committee in the School of Nursing and Public Health at the University of KwaZulu-Natal. Permission to conduct the study was granted by the KwaZulu-Natal Department of Health, as well as hospital management.

Results

The inclusion criteria were met by 354 patients. Nearly 70% (247) were women (Table I). The median age at initiation of HAART was 36 years, and 92.1% (326) of patients were aged < 50 years at the time of HAART initiation. All of the patients were initiated on an NNRTI-based regimen. Ninety-four per cent (334) of the patients had a CD4 count of ≤ 200 cells/ul at baseline, while only 0.3% (1) had a baseline CD4 count of > 350 cells/ul. Other baseline characteristics are shown in Table I.

The median interquartile range CD4 T-cell count increased from 92 cells/ul (53-152.5 cells/ul) at the time of HAART initiation to 429 cells/ul (309.5-590.3 cells/ul) by the third year. The median CD4 T-cell count at the sixth month, first year, second year and third year post-HAART initiation is displayed in Figure I. Analysis of CD4 T-cell count increase in the first six months revealed an increase of 106 cells/ul (45-177 cells/ul), while increases in the subsequent intervals became smaller, 72 cells/ul (13-144 cells/ul) in the second year, and 62 cells/ul (−15 to 133 cells/ul) in the third year. The overall increase in median CD4 T cells over three years was 325 cells/ul (−8 to 1 365 cells/ul). The increase in CD4 T cells in the first year was 184 cells/ul (109-287 cells/ul). The increase in CD4 T-cells according to the baseline CD4 strata is displayed in Table II.

Table I: The baseline characteristics of 354 patients who met the inclusion criteria

Characteristics	Values
Female	247 (69.8)
Age (years) [median (25-75%)]	36 (31-42)
< 50 years	326 (92.1)
An NNRTI-based regimen	354 (100)
Hepatitis B virus co-infection	22 (6.21)
Pulmonary tuberculosis co-infected on treatment	63 (17.8)
AIDS-defining illness at baseline	26 (7.3)
Baseline CD4 count (cells/ul) [median (25-75%)]	92 (53-152.5)
Number with baseline CD4 cell count ≤ 50 cells/ul	85 (24)
Number with baseline CD4 cell count 51-100 cells/ul	108 (30.5)
Number with baseline CD4 cell count 101-200 cells/ul	141 (39.8)
Number with baseline CD4 cell count > 200 cells/ul	20 (5.7)

AIDS: acquired immune deficiency syndrome, CD4: cluster of differentiation 4, NNRTI: non-nucleoside reverse transcriptase inhibitor
Values are n (%) unless otherwise stated
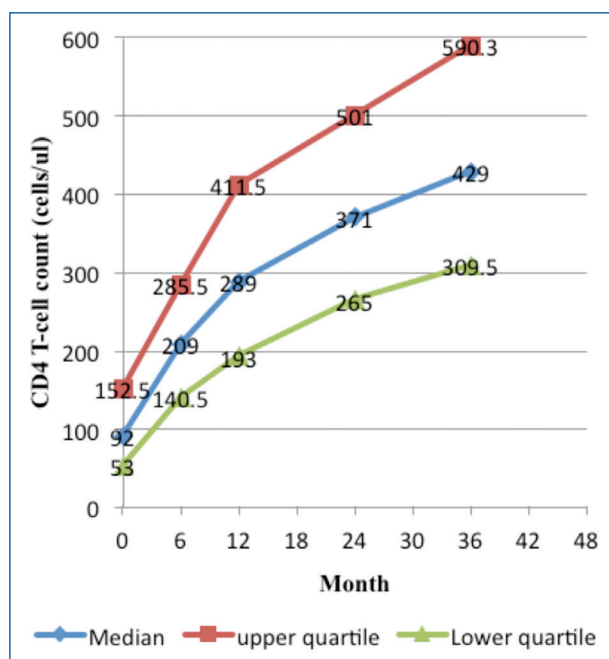
CD4: cluster of differentiation 4
Figure I: Evolution of CD4 T cells during the three years of virological suppression on highly active antiretroviral therapy

The overall increase in the median CD4 T-cell count after three years of virological suppression on HAART was greater in females (349 cells/ul) than in males (273 cells/ul). The overall increase for other baseline stratification variables is displayed in Table III. At the last determination (after three years of virological suppression on HAART), 37.3% (132) of patients had a CD4 count ≥ 500 cells/ul and 6.8% (24) had a CD4 count of < 200 cells/l. For the non-responders at baseline, 87.5% (21) had a baseline CD4 count of < 100 cells/ul, 12.5% (3) had an AIDS-defining illness, 16.7% (4) had hepatitis B co-infection and 8.3% (2) had pulmonary tuberculosis. According to the baseline CD4 strata (≤ 50, 51-100,101-200 and > 200 cells/ul) 27.1% (23), 27.8% (30), 49.6% (70) and 45% (9), respectively, had a CD4 count ≥ 500 cells/ul at the last determination, while 12.9% (11), 9.3% (10), 2.1% (3) and 0% (0), respectively, had a CD4 count < 200 cell/ul at the last determination. Further analysis carried out using non-parametric test statistics to compare the overall increase between baseline stratification variables showed only the difference in the overall increase in median CD4 count in sex stratum to be statistically significant (p-value < 0.05). Other results are displayed in Table III.

Further analysis was performed to determine the number of patients with a CD4 T-cell count < 500 cells/ul and ≥ 500 cells/ul at the last determination by using only two baseline CD4 T-cell strata viz. a CD4 T-cell count < 100 cells/ul and a CD4 T-cell count ≥ 100 cells/ul. This was carried out in view of some strata having small numbers. The results are documented in Table IV.

Discussion

Data from three previous studies suggested a median increase of approximately 200-300 cells/ul after 3-4 years of HAART.[9] The response to HAART in this study was good when compared to the aforementioned studies, with an overall increase of 325 cells/ul. A study by Tarwater et al suggested that relative immune reconstitution was greater in patients with a lower baseline CD4 T-cell count.[19] The majority (94%) of patients in this study had a baseline CD4 T-cell count of ≤ 200 cells/ul, which could explain the good response.

The median increase in the CD4 T-cell count following HAART intitation was greatest in the first six months and greater in the first year, with a smaller but continued increase in the subsequent intervals up to the third year. This pattern of increase was also observed for the baseline CD4 strata, except for the highest stratum that had a lesser increase in the first six months than the others, but this was not statistically significant

Table II: Median increase in CD4 T-cell count (cells/ul) over time, and the overall increase in CD4 T-cell count (cells/ul) over three years, according to the baseline CD4 strata

Baseline CD4 strata (cells/ul)	First six months	Six months to the first year	First year	Second year	Third year	Overall increase
≤ 50	108 (64 to 181)	67 (21 to 136)	191 (123 to 273)	77 (21 to 148)	72 (2 to 126)	346 (248 to 513)
51-100	108 (46 to 180)	64 (22 to 138)	164 (101 to 294)	52 (13 to 199)	63 (−18 to 144)	301 (198 to 431)
101-200	103 (42 to 186)	88 (20 to 155)	204 (112 to 330)	73 (−3 to 148)	60 (−14 to 147)	335 (226 to 539)
> 200	49 (15 to 137)	67 (24 to 136)	142 (84 to 200)	106 (4 to 233)	15 (−105 to 175)	246 (121 to 404)

CD4: cluster of differentiation 4
The figures in brackets represent the interquartile range

Table III: Non-parametric analysis of the overall increase in median CD4 T-cell count (cells/ul) for baseline stratification variables, using the Mann-Whitney U test for variables with two levels, and the Kruskal-Wallis for those with more than two levels

Characteristics	Value (25-75%)	p-value
Gender		
Male	273 (165-421)	< 0.001
Female	349 (235-536)	
Age (years)		
< 50	325 (214-479)	0.952
≥ 50	324 (195-512)	
Hepatitis B		
Hepatitis B virus co-infection	280 (136-447)	0.232
No hepatitis B virus co-infection	325 (215-480)	
Pulmonary tuberculosis		
Pulmonary tuberculosis* co-infection	315 (218-423)	0.896
No pulmonary tuberculosis co-infection	325 (211-493)	
AIDS		
AIDS at baseline	272 (157-404)	0.090
No AIDS at baseline	328 (216-485)	
CD4 strata*		0.084

AIDS: acquired immune deficiency syndrome
* Overall increase for baseline CD4 strata, already displayed in Table II

Table IV: CD4 T-cell count at the last determination using only two baseline strata

Baseline CD4 T-cell count	CD4 T-cell count at year three (percentage)		p-value
	< 500 cells/ul	≥ 500 cells/ul	0.013
< 100 cells/ul (n = 192)	139 (72.4)	53 (27.6)	
≥ 100 cells/ ul (n = 162)	83 (51.2)	79 (48.8)	

(p-value 0.086). The stratum with a baseline CD4 T-cell count between 51 and 100 cells/ul also showed an unusually greater increase in the third year, compared to that in the second year, but this was also not found to be statistically significant (p-value 0.108). This biphasic pattern of a greater rise in the first few months, and a subsequent lesser rise, has been described in other studies.[5,8,20,21]

Despite the good response to HAART, the CD4 T-cell count in this group did not reach the normal value of 500 cells/ul, which represents the lower boundary of normal.[3] A study on incompletely virologically suppressed patients by Tarwater et al revealed a CD4 T-cell count of 410 cells/ul at the last determination from a baseline of 249 cells/ul, with no further increase following 2-3.5 years of HAART.[19] In a study on 210 patients by Michael et al, CD4 T-cell count was found to have reached a plateau at the third year of follow-up, with a value of 380 cells/ul from a baseline of 270 cells/ul.[22] In the latter study, virological suppression was maintained at < 20 copies/ml.

With regard to the reconstitution of CD4 T cells to normal levels, only 37.3% had a CD4 T-cell count ≥ 500 cells/ul at the last determination, while 6.8% had a CD4 T-cell count < 200 cells/ul, and were still at risk of opportunistic infections at the end of the three years. This was similar to observations in a cohort of 861 patients, in whom 50% had a CD4 T-cell count > 500 cells/ul, and 12% had a CD4 T-cell count < 200 cells/ul.[9] Conversely, a study by Kaufmann et al on virologically suppressed patients showed that 74% had a CD4 T-cell count > 500 cells/ul, and only 2% had CD4 T-cell count < 200 cells/ul.[23] The difference between that study and this one, both of which adopted virological suppression as an inclusion criterion, could be because of the former's higher baseline CD4 T-cell count (325 cells/ul).

Although studies have shown that virological suppression is the major determinant in the extent and duration of immune reconstitution,[10,24] several studies have also shown that those who commence HAART at a lower CD4 T-cell count are less likely to attain normal levels, even after 10 years of effective ARV therapy.[8,9,15,22,25] In this study, only 27.6% (53) with a CD4 T-cell count < 100 cells/ul at baseline attained normal levels of CD4 T-cell count at the last determination when compared to 48.8% (79) of those with a CD4 T-cell count ≥ 100 cells/ul. This difference was statistically significant (p-value 0.013).

Of all of the stratification variables, only the female sex was associated with a positive increase in CD4 T-cell count in this study. This was also reported by Maman et al and Giordano et al.[26,27] While similar findings were reported only in the first six months in the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort, other studies showed no association.[6-8,25] It has been suggested that women might have a greater thymic output of naïve/memory CD4 T cells following HAART than men, and may also replenish their peripheral CD4 T cells faster than males.[27,28]

This study involved a review of clinical notes over a short time. A longer period of review is required to confirm if immune reconstitution improved beyond the findings of this study. Other limitations to consider include the strict inclusion criteria which limited the number of files that were reviewed. A major strength of this study was the chosen cut-off for virological suppression, since currently, the aim of HAART is to suppress the viral load to < 50 copies/ml.[7]

Conclusion

In summary, although the response of patients who remained virologically suppressed in this hospital's ARV clinic was good, the median CD4 T-cell count at the last determination did not reach normal levels. Those who were initiated with a CD4 T-cell count < 100 cells/ul were less likely to attain a normal level. This supports the WHO and the South African ARV guidelines that suggest the initiation of HAART at a CD4 T-cell count of < 500 and ≤ 350 cells/ul, respectively. A concerted effort must be made to identify patients who are HIV-positive and to initiate HAART at a level that is much higher than what is currently happening in clinical practice. The baseline median CD4 T-cell count of 92 cells/ul, demonstrated in this study, is far too low for the initiation of HAART. In addition, community awareness of services offered needs to be upscaled to enable patients to access care early. Additional research is required to investigate risk factors and long-term mortality in non-responders.

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Conflict of interest

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them when writing this paper.

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